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EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 12/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,476	PRENDERGAST ET AL.	
	Examiner	Art Unit	
	Raymond J Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *21,30-62 and 65-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22-29,63 and 64* is/are rejected.

7)☒ Claim(s) *6, 15, 16 and 63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12152004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1-71 ARE PRESENTED FOR EXAMINATION

Applicants' "Response to Restriction and Election of Species Requirements" filed November 19, 2004 and Information Disclosure Statement filed July 2, 2003 has been received and entered into the application.

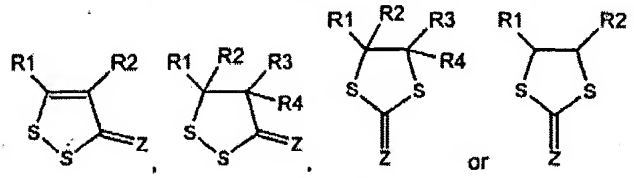
As reflected by the attached, completed copies of form PTO-1449 (3 pages total), the cited references have been considered by the Examiner.

Election/Restriction

Applicant's election with traverse of Group I (claims 1-44 and 62-64) and election of oltipraz as the species of active agent; compounds which chelate with, or form a complex with, one or more divalent or trivalent metal ions as a subgenus within the group of compounds recited in claim 1; and neurodegenerative diseases as the therapeutic use in the reply filed on November 19, 2004 is acknowledged. The traversal is on the grounds that a serious burden ***would not*** be placed on the Examiner by searching for and examining the entire application as filed.

Applicant's traverse has been carefully considered, but is not found persuasive because of the reasons as set forth in the previous Office action dated May 21, 2004. Further, it is the Examiner's position that a search and examination of the entire application as filed would impose a serious burden on the Examiner such that a quality examination could not be reasonably accomplished. In particular, the claims as presented contain numerous combinations of possible compounds and therapeutic uses. Claim 1 is representative and reads:

1. A method to treat, prevent or slow the progression of a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, malaria, a leishmania parasite infection or a trypanosome infection, or to ameliorate a symptom thereof, or to treat aluminum intoxication, reperfusion injury, or to reduce the level of iron or to reduce free transition metal ion levels in the body or in certain body compartments, in a subject in need thereof, the method comprising administering to the subject or delivering to the subject's tissues a therapeutically effective amount of a compound having the formula



and oxides, derivatives and metabolites thereof, wherein

Z is S, O, NR, R_2 or CR_2;

R is -H, -OH, C_1-C_5 alkyl, C_1-C_5 alkoxy or C_1-C_5 alkoxycarbonyl;

R_2, together with the atoms to which it is bonded, comprises a spiro or fused ring to yield a bicyclic or tricyclic compound, which is saturated or unsaturated, heterocyclic or carbocyclic and wherein the rings are all optionally substituted 5-, 6-, 7- or 8-membered rings, with substituents optionally selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_3H, -OH and halogen;

R1, R2, R3 and R4 independently are -H, -alkyl, -aryl, -alkylaryl, a heterocycle, a halogen, -alkoxycarbonyl (C_1-C_5) or -carboxyl,

wherein either alkyl is a C_1-C_{10} linear or branched chain, saturated or unsaturated moiety, which is optionally substituted by 1, 2 or more independently selected ether (-O-), halogen, alkyl (C_1-C_5), -OH, alkoxy (C_1-C_5), alkoxycarbonyl, (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono- or dialkylamino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), or benzenoid aryl, and

wherein the -aryl and -alkylaryl substituent for R1, R2, R3 and R4 comprises a benzenoid group (C_6-C_{14}), wherein the benzenoid group is optionally substituted with 1, 2 or more independently selected -SO_3H, halogen, alkyl (C_1-C_5), -OH, alkoxy (C_1-C_5), alkoxycarbonyl, (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono- or dialkylamino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), and

wherein the heterocycle is defined as any 4, 5 or 6 membered, optionally substituted heterocyclic ring, saturated or unsaturated, containing 1-3 ring atoms selected from N, O and S, the remaining ring atoms being carbon; and wherein said substituents on said aryl or said heterocyclic are selected from the group consisting of halogen, alkyl (C_1-C_5), hydroxyl, alkoxy (C_1-C_5), alkoxycarbonyl (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono and dialkyl amino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), benzenoid, aryl, cyano, nitro, haloalkyl (C_1-C_5), alkisulfonyl (C_1-C_5), or sulfonate, or

one of R1 and R2 and one of R3 and R4 together with the carbon atoms to which they are attached comprise a fused bicyclic or tricyclic compound, which is saturated or unsaturated, heterocyclic or carbocyclic and wherein the rings are all optionally substituted 5-, 6-, 7- or 8-membered rings, with substituents optionally selected from alkyl, alkoxy, -SO_3H, -OH and halogen, or

R1 and R2 together or R3 and R4 together independently are oxime (=NOH).

Each of the above disease states/disorders/conditions require separate, independent considerations regarding etiology, pathophysiological manifestations, pharmacological treatment options and therapeutic outcome goals. Further, the claim requires three different therapeutic objectives for each disease state/disorder/condition, i.e., "treat", "prevent" or "slow the progression of". Additionally, for each of the above treatment/objective combination, the claim provides for the administration of four different type of compounds, i.e., two types of 1,2-dithiol compounds and two types of 1,3-dithiol compounds, each of which may be substituted in a multitude of ways.

When considering not only the sheer number of combinations and/or permutations of treatment objectives and therapeutic agents represented in the claims as originally filed, but also the fact that a finite quantity of time is provided to examine the present application, it is clear that a search and examination of all claimed subject matter would place a serious, undue burden on the Examiner.

Therefore, for the reasons above and of record, the requirement is still deemed proper and is therefore made **FINAL**.

Claims 21, 30-62 and 65-71 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

The claims corresponding the elected subject matter are 1-20, 22-29, 63 and 64 and such claims are herein acted on the merits. The species of the therapeutic objective that is herein examined is "a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder". While Applicants have elected neurodegenerative disorders as the species, the Examiner has expanded the scope of this species to include those species which represent a single grouping of therapeutic objectives which are patentably distinct from the other claimed therapeutic objectives.

Claim Objections

Claim 16 is objected to because at line 1, "compound micronized" should read as --- compound is micronized---.

Claim 63 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel the claim, amend the claim to place it in proper dependent form, or rewrite the claim in independent form.

Claim 63 depends from claim 1 or 11 solely for the purpose of identifying the compounds to be administered. This is not proper because by relying on claim 1 or 11, claim 63 incorporates not only the compounds of claim 1 or 11, but the entire method of claim 1 or 11 as

well. Claim 63 does not further limit claim 1 or 11 in any manner and thus its dependency therefrom is improper.

Claims 6 and 15 are objected to because "type 11 diabetes" should read ---type II diabetes---.

Claim Interpretation

Claims must be given their **broadest reasonable** interpretation consistent with the supporting description. See *In re Hyatt*, 54 USPQ2d 1664,16678 (Fed. Cir. 2000). Words and phrases in the claims must be given their "plain meaning" as understood by one having ordinary skill in the art unless defined by applicant in the specification with "reasonable clarity, deliberateness and precision". (MPEP 2111.01).

Here, Applicants have not defined the terms "a neurodegenerative disorder" or "a degenerative disorder". The term "a degenerative disorder" will be interpreted as including any and all disorders resulting from a deterioration; a worsening of mental or physical qualities; or a retrogressive pathological change in cells or tissues, in consequence of which the functions may be impaired or destroyed (See Stedman's Medical Dictionary at page 406, entry for "degeneration"). The term "a neurodegenerative disorder" will be interpreted as above for "a degenerative disorder" to the extent that the degeneration is that of nervous system tissues.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-23, 25-29, 63 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 8-23, 25-29, 63 and 64 are considered indefinite because in claims 1, 6, 11, 15, 25, 63 and 64, the terms "degenerative", as employed in the expressions "a degenerative disorder" and "related", as used in the expressions "a degenerative-related disorder", "a neurodegenerative-related disorder" and "related degenerative disorders", are not defined in the claims and the specification does not provide a standard for ascertaining the requisite qualitative nature of the "degeneration" or "relationship" such that one of ordinary skill in the art would be reasonably apprised of what degenerative disorders, other than those expressly set forth, are intended to be covered by the present claims. Absent such a standard, the terms "degenerative" and "related" would invite subjective interpretations as to the metes and bounds of the subject matter of the present claims which is not proper under 35 U.S.C. § 112, second paragraph.

In order to overcome this point of rejection, applicants may wish to consider amending the claims by deleting the expressions containing "related" as well as the expression "a degenerative disorder". In the place of these expressions, applicants should expressly recite the specific disorders for which patent protection is sought.

In claims 63 and 64, the expressions "*Use in* a method of treatment" (claim 63, emphasis added) and "*Use of* a D-amino acid oxidase inhibitor" (claim 64, emphasis added) connote that the subject matter for which Applicants are seeking patent protection includes not only a method of treatment of degenerative or related disorders which comprises administering an effective amount of the claim designated compounds to a subject in need thereof (claim 63) or a method

for the treatment or prevention of a degenerative disorder comprising the administration of an effective amount of a D-amino acid oxidase inhibitor to a mammal in need thereof (claim 64), but another, undefined process, i.e., "use", as well. The mere recitation of "use", however, does not particularly point out the metes and bounds of that subject matter.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." (MPEP 2173).

Because the expression "use" has not been adequately defined in either the claims or specification, it is the Examiner's position that the public would not be informed of the boundaries of what constitutes infringement of the present claims and thus the claims do not meet the requirements of 35 U.S.C. § 112, second paragraph.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20, 22-29, 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating or slowing the progression of a degenerative or neurodegenerative disorder, does not reasonably provide enablement for the prevention of a degenerative or neurodegenerative disorder. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Burden on the Examiner for Making a Rejection Under 35 U.S.C. § 112 First Paragraph

As set forth in *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contain therein which must be relied on for enabling support*; assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in specification is truly enabling." (emphasis added).

Here, the objective truth of the statement that a degenerative or neurodegenerative disorder can be prevented is doubted because the art (see the references relied upon *infra*) teaches that, at best, the prevention of neurodegenerative diseases is merely a possibility and not a treatment outcome that can be accomplished with a reasonable degree of certainty. Further, the term "preventing" is synonymous with the term "curing" and both circumscribe methods of absolute success. Because absolute success is not reasonably possible with most diseases/disorders, especially those having an etiology and pathophysiological manifestations as complex/poorly understood as a degenerative disease/disorder, neurological or otherwise, such as Alzheimer's disease, the specification, which lacks an objective showing that a degenerative disease/disorder, neurological or otherwise, such as Alzheimer's disease, can actually be prevented, is viewed as lacking an enabling disclosure of the same.

Concerning the state of the art of the prevention of degenerative disorders, including

neurodegenerative disorders such as Alzheimer's disease, the teachings below establish the basis for the Examiner's doubt of the objective truth of the statement that the presently claimed active agents could be used to successfully prevent a degenerative or neurodegenerative disorder, (the quoted portions below are taken from the single-paragraph Medline Abstract cited by the Examiner). In particular, the references make clear that in the art, the prevention of degenerative diseases of the type claimed was, at the very best, uncertain and unpredictable.

It is noted that two of the references, i.e., Jellinger and Lockhart et al., have publication dates which are after the earliest priority date of the present application, i.e., the earliest priority date of the present application is April 13, 2000 while Jellinger was published January-March 2001 and Lockhart et al. was published January-February 2003. The Examiner's reliance on such references is proper however. "References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made. *Ex parte Erlich*, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992.)."(emphasis added)(MPEP 2124).

James et al. teach "Understanding the functional aspects of neuronal nicotinic receptor subtypes *may* lead to successful therapeutic treatments or disease *preventative strategies for neurodegenerative disorders*."(emphasis added);

Prasad et al. teach "*In spite of extensive basic and chemical research* on Parkinson's disease and Alzheimer's disease, ***no preventive*** *or long-term effective treatment strategies* ***are available***."(emphasis added);

Jellinger teach "In conclusion, although many in vivo and in vitro data are in favor of apoptosis involvement in neurodegenerative processes, there is considerable evidence that very complex events *may* contribute to neuronal death with possible repair mechanisms, the elucidation of which *may prove useful for future* prevention and therapy of neurodegenerative disorders."(emphasis added); and

Lockhart et al. teach "Based on current population projections it has been estimated that by 2050 the number of individuals over 65 will increase to 1.1 billion worldwide and ***as a consequence, the number of cases of dementia to 37 million.*** Faced with such an enormous public health and socio-economic burden it is evident that *the importance of therapeutic intervention* ***aimed at*** *either finding a cure or preventing disease progression cannot be overstated*"(emphasis added).

Summary

As the cited art and discussion above establish, practicing the claimed method in the manner disclosed by Applicants would not imbue the skilled artisan with a reasonable expectation that the prevention of a degenerative or neurodegenerative disorder could be achieved. In order to actually achieve the prevention of a degenerative or neurodegenerative disorder, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize, and Applicants have failed to demonstrate, that a degenerative or neurodegenerative disorder could actually be prevented, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 1-20, 22-29, 63 and 64 are deemed properly rejected.

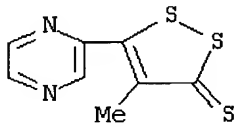
Overcoming the Above Rejection

The Examiner recommends that Applicants delete the concept of prevention from claims 1-20, 22-29, 63 and 64 in order to overcome the present rejection.

Scope and Content of the Claims

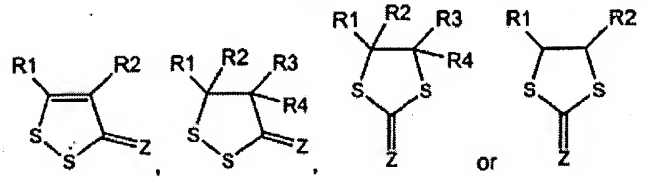
Consistent with the restriction/election of species requirement made by the Examiner and the subsequent election by Applicants, the present claims are examined to the extent that they are directed to a method to treat, prevent or slow the progression of a degenerative disorder, a

neurodegenerative disorder, a degenerative-related disorder or a neurodegenerative-related disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of oltipraz, i.e., 4-methyl-5-pyrazinyl-3H-1,2-Dithiole-3-thione, which is represented by the structure:



Claim 1 is representative of the claimed method and reads:

1. A method to treat, prevent or slow the progression of a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, malaria, a leishmania parasite infection or a trypanosome infection, or to ameliorate a symptom thereof, or to treat aluminum intoxication, reperfusion injury, or to reduce the level of iron or to reduce free transition metal ion levels in the body or in certain body compartments, in a subject in need thereof, the method comprising administering to the subject or delivering to the subject's tissues a therapeutically effective amount of a compound having the formula



and oxides, derivatives and metabolites thereof, wherein

Z is S, O, NR, R_2 or CR_2;

R is -H, -OH, C_1-C_5 alkyl, C_1-C_5 alkoxy or C_1-C_5 alkoxycarbonyl;

R_2, together with the atoms to which it is bonded, comprises a spiro or fused ring to yield a bicyclic or tricyclic compound, which is saturated or unsaturated, heterocyclic or carbocyclic and wherein the rings are all optionally substituted 5-, 6-, 7- or 8-membered rings, with substituents optionally selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_3H, -OH and halogen;

R1, R2, R3 and R4 independently are -H, -alkyl, -aryl, -alkylaryl, a heterocycle, a halogen, -alkoxycarbonyl (C_1-C_5) or -carboxyl,

wherein either alkyl is a C_1-C_{10} linear or branched chain, saturated or unsaturated moiety, which is optionally substituted by 1, 2 or more independently selected ether (-O-), halogen, alkyl (C_1-C_5), -OH, alkoxy (C_1-C_5), alkoxycarbonyl, (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono- or dialkylamino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), or benzenoid aryl, and

wherein the -aryl and -alkylaryl substituent for R1, R2, R3 and R4 comprises a benzenoid group (C_6-C_{14}), wherein the benzenoid group is optionally substituted with 1, 2 or more independently selected -SO_3H, halogen, alkyl (C_1-C_5), -OH, alkoxy (C_1-C_5), alkoxycarbonyl, (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono- or dialkylamino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), and

wherein the heterocycle is defined as any 4, 5 or 6 membered, optionally substituted heterocyclic ring, saturated or unsaturated, containing 1-3 ring atoms selected from N, O and S, the remaining ring atoms being carbon; and wherein said substituents on said aryl or said heterocyclic are selected from the group consisting of halogen, alkyl (C_1-C_5), hydroxyl, alkoxy (C_1-C_5), alkoxycarbonyl (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono and dialkyl amino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), benzenoid, aryl, cyano, nitro, haloalkyl (C_1-C_5), alkisulfonyl (C_1-C_5), or sulfonate, or

one of R1 and R2 and one of R3 and R4 together with the carbon atoms to which they are attached comprise a fused bicyclic or tricyclic compound, which is saturated or unsaturated, heterocyclic or carbocyclic and wherein the rings are all optionally substituted 5-, 6-, 7- or 8-membered rings, with substituents optionally selected from alkyl, alkoxy, -SO_3H, -OH and halogen, or

R1 and R2 together or R3 and R4 together independently are oxime (=NOH).

Legal Standard for Anticipation/Inherency Under - 35 USC § 102

To anticipate a claim under 35 U.S.C. § 102, a single prior art reference must place the invention in the public's possession by disclosing each and every element of the claimed invention in a manner sufficient to enable one skilled in the art to practice the invention. *Scripps Clinic & Research Foundation v. Genetech, Inc.,* 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1001 (Fed. Cir. 1991); *In re Donahue,* 766 F2d531, 533, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). To anticipate, the prior art must either expressly or inherently disclose every limitation of the claimed invention. *MEHL/Biophile Int'l Corp. v. Milgraum,* 192 F.3d 1362, 1365, 52 U.S.P.Q.2d 1303, 1303 (Fed. Cir. 1999) (citing to *In re Schreiber,* 128 F.3d 1473, 1477, 44 U.S.P.Q. 1429, 1431 (Fed. Cir. 1997)); *Atlas Powder Co. v. Ireco Inc.,* 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943, 1946 (Fed. Cir. 1999). To inherently anticipate, the prior art must necessarily

function in accordance with, or include, the claimed limitations. *MEHL/Biophile*, 192 F.3d at 1365, 52 U.S.P.Q.2d at 1303. However, it is not required that those of ordinary skill in the art recognize the inherent characteristics or the function of the prior art. *Id.* Specifically, discovery of the mechanism underlying a known process does not make it patentable.

Multiple Reference 35 U.S.C. § 102 Rejections

This Office action contains a rejection under 35 U.S.C. § 102 based on multiple references. The additional reference is relied on to explain the meaning of a term used in the primary reference or to show that a characteristic not disclosed in the primary reference is inherent. Accordingly, the Examiner's reliance on multiple references is proper. "Normally, only one reference should be used in making a rejection under 35 U.S.C. § 102. However, a 35 U.S.C. § 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"

(B) Explain the meaning of a term used in the primary reference; or

(C) Show that a characteristic not disclosed in the reference is inherent." (See MPEP § 2131.01).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I Claims 1-20, 22-29, 63 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Shapiro (U.S. Patent No. 5,668,117, cited by Applicants).

Shapiro teaches a method for the treatment of neurodegenerative diseases including motor and sensory neuropathies, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's pre-senile and senile dementia, Down's syndrome and polyneuropathy (e.g., see col. 1, lines 22-30:

> **This invention relates to the clinical treatment of neurodegenerative diseases, including hereditary motor and sensory neuropathies (HMSN, also known as Charcot-Marie-Tooth disease), diabetic polyneuropathy, Alzheimer's presenile and senile dementia, Down's syndrome, Parkinson's disease, olivopontocerebellar atrophy, Huntington's disease, amyotrophic lateral sclerosis, age-onset neurological deterioration, alcoholic polyneuropathy, tinnitus, multiple sclerosis, and pathophysiologically symptomology.**).

Shapiro further teach that the method comprises administering to a subject in need thereof a composition which may comprise an effective amount of oltipraz as an additional active agent (not precluded because the present claims recite "comprising") and a pharmaceutically acceptable carrier (see the abstract; col. 14, line 65 – col. 15 line 5; col. 16, line 5; and the compositions taught in claims 1-5, 8, 9 and 12-25).

Shapiro fails to expressly disclose the following claim limitations:

(i) "a degenerative disorder" "a neurodegenerative-related disorder" (e.g., claim 1), "related degenerative disorders" (e.g., present claim 1 and claim 6, last line);

(ii) "the compound chelates with, or forms a complex with, one or more divalent or trivalent metal ions, whereby the divalent or trivalent ions in the subject's cells or tissues are redistributed or sequestered such that the ions are limited in their capacity to participate in unwanted reactions such as the Fenton reaction"(e.g., present claims 3 and 4);

(iii)"said compound is a D-amino acid oxidase inhibitor and cellular degeneration is slowed or arrested" (e.g., present claim 8); or

(iv) "said compound enhances one or more phase II detoxification enzymes" (e.g., present claims 9 and 10).

However, for the following reasons, such limitations do not impart patentable moment to the claimed subject matter.

Limitation (i) is met by the disclosure of Shapiro because the patentee expressly discloses "neurodegenerative diseases" which are clearly types of "degenerative" diseases. Also, they are "related degenerative disorders" and "a neurodegenerative-related disorder" because by being neurodegenerative diseases, they share a common "degenerative" characteristic and thus are related.

Limitations (ii), (iii) and (iv) would necessarily be present, i.e., inherent, in the method taught by Shapiro because such in both the present claims and the method of Shapiro, the same active agent, i.e., oltipraz, is administered to the same subject and would exist in the same physiological environment and thus it must necessarily follow that the compound would possess the same characteristics as presently claimed, whether expressly disclosed in the reference or not.

II Claims 1- 20, 22-29, 63 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Schneider et al. (WO 98/27970, cited by Applicants), Stedman's Medical Dictionary and Remington's Pharmaceutical Sciences ("Remington's", cited by the Examiner).

Schneider et al. teach a method for treating or slowing the progression of diseases in which pathological damage is caused by free radicals which comprises administering to a patient in need thereof, and thus necessarily, i.e., inherently, to the cells of the patient, a therapeutically

effective amount of a pharmaceutical composition which comprises oltipraz and a pharmaceutically acceptable carrier (see the abstract; page 6, lines 15-22 and line 31 – page 7, line 7; page 12, line 33; page 13, line 32 – page 15, line 22; and claims 1, 2, 8 and 9 at pages 39-40).

The specific diseases claimed by Applicants (and encompassed by the claimed expressions "a degenerative disorder", "a neurodegenerative disorder", "a neurodegenerative-related disorder", "related degenerative disorders") which are disclosed by Schneider et al. are Alzheimer's disease and Parkinson's disease (page 1, line 18).

Schneider et al. further disclose that the activity of the enzyme glutathione S transferase is increased (see page 7, lines 14-16 and compare to present claims 9, 10 18, 19, 28 and 29). Schneider also discloses that the pharmaceutical composition may comprise carriers such as water (see page 14, line 4 and compare to present claims 16 and 26).

Schneider et al. fail to expressly disclose the following claim limitations:

(i) "cerebropathy" or "memory loss" (e.g., present claim 6)

(ii) "the compound chelates with, or forms a complex with, one or more divalent or trivalent metal ions, whereby the divalent or trivalent ions in the subject's cells or tissues are redistributed or sequestered such that the ions are limited in their capacity to participate in unwanted reactions such as the Fenton reaction"(e.g., present claims 3 and 4);

(iii)"said compound is a D-amino acid oxidase inhibitor and cellular degeneration is slowed or arrested" (e.g., present claim 8);

(iv) "said compound enhances one or more phase II detoxification enzymes" (e.g., present claims 9 and 10); or

(v) "a liquid excipient suitable for ophthalmic pharmaceutical formulations" (present claim 16).

However, for the following reasons, such limitations do not impart patentable moment to the claimed subject matter.

Parkinson's disease and Alzheimer's disease are both diseases of the brain and thus meet the claimed limitations of "cerebropathy" because in Stedman's, it is indicated that "cerebropathy" means "encephalopathy" (page 280, col. 1) and "encephalopathy" is defined as "any disease of the brain" (page 508, col. 1). Also, because Alzheimer's disease involves memory impairment (Stedman's at page 410, col. 2 "dementia, Alzheimer's d.") such would meet the claimed limitation for "memory loss".

Limitations (ii), (iii) and (iv) would necessarily be present, i.e., inherent, in the method taught by Schneider et al. because not only do they expressly disclose that the activity of the enzyme glutathione S transferase is increased, but also because in both the present claims and the method of Schneider et al., the same active agent, i.e., oltipraz, is administered to the same subject and would exist in the same physiological environment and thus it must necessarily follow that the compound would possess the same characteristics as presently claimed, whether expressly disclosed in the reference or not.

Schneider et al. expressly disclose that the pharmaceutically acceptable carrier may be a phosphate-buffered saline solution (page 14, line5). This would inherently meet the claimed limitation of "a liquid excipient suitable for ophthalmic pharmaceutical formulations" (present claim 16) because Remington's shows that (a) a phosphate buffer and (b) saline solution are both

recommended for extemporaneous preparation of ophthalmic solutions (page 1503, col. 2, section B2 under the heading "Extemporaneous Procedures").

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20, 22-29, 63 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Shapiro or Schneider et al. in view of Girijavallabhan et al. (U.S. Patent No. 5,559,133, cited by the Examiner).

The difference between the above and the claimed subject matter lies in that neither Shapiro nor Schneider et al. disclose a pharmaceutical composition comprising micronized oltipraz and a substance selected from phosphatidylcholine, diphosphatidylcholine, vitamin E, a cyclodextrin, magnolol or a microbial preservative (see present claim 16).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(1) Shapiro teaches that the compositions taught therein may also contain one or more of an antioxidant such as vitamin E (a.k.a. alpha tocopherol) and/or phosphatidylcholine (see, e.g., col. 36, line 35 and col. 66, line 46). The skilled artisan would have been motivated to include vitamin E and/or phosphatidylcholine in order to gain the advantages of doing so as taught by Shapiro, i.e., additional therapeutic efficacy. Also, because "phosphatidylcholine" is taught in general, the selection of any particular phosphatidylcholine-type compounds, such as diphosphatidylcholine, would appear to have been a matter well within the purview of one of ordinary skill in the art.

(2) Schneider et al. teach "using standard pharmaceutically-acceptable ingredients, if required, i.e., adjuvants, excipients, diluents or carriers" (page 14, lines 1-3, emphasis added) and "preservatives" in particular (page 14, line 30). The selection of any specific pharmaceutically acceptable ingredient and particle form, such as micronized, from those known such as a cyclodextrin (see Girijavallabhan et al. at col. 11, lines 31-58) or preservatives, including a microbial preservative, would have been a matter well within the purview of the skilled artisan and the artisan would have been motivated to make such a selection in order to provide the patient with the most effective, elegant, sterile product possible.

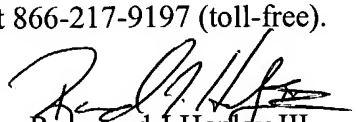
The Examiner can find no teaching or suggestion to include magnolol in a composition that is employed in the presently claimed method. Stogniew et al. (U.S. Patent No. 6,814,987) is cited to show the general state of the art concerning magnolol-containing compositions.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Raymond J Henley III
Primary Examiner
Art Unit 1614

December 19, 2004